

**DOCKET NO.: 17637
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PATENT

REMARKS

Upon entry of this response, claims 1-6 and 8-12 will be pending. Claims 1 and 6 have been amended to include the feature "to a patient in need thereof". Amended claims 1 and 6 are fully supported by the specification at, for example, page 22, lines 5-18, which states: "A method for treating a skin disorder according to the present invention can comprise the step of local administration of a botulinum toxin to a patient with a skin disorder to thereby alleviate the skin disorder." New claim 12 is fully supported by the specification at, for example, page 1, lines 20-21, of the specification. No new matter is added.

As a preliminary matter, Applicant acknowledges the Office Action's comments regarding the missing two references: (CI) Bushara K., Otolaryngol Head Neck Surg 1996; 114(3):507; and (CM) Dugan et al. Mov Disord, 10(3);376:1995. Applicant is enclosing these references herewith.

Claims 1-6, 9 and 10 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,670,484 and EP 0 845 267 B1 (hereinafter "the Binder reference"). The Office Action alleges that disclosure of "lesion" by the Binder reference is the equivalent of the claimed "ulcer" feature. Applicant respectfully disagrees.

The type of "lesion" that the Binder reference discloses relates to cutaneous cell-proliferative disorders, e.g., psoriasis. A cutaneous cell-proliferative disorder is different from an ulcer. For example, a psoriasis lesion (a cutaneous cell-proliferative disorder) is "papules and plaques, sharply marginated with marked silvery-white scale". Exhibit 1: Color Atlas and Synopsis of Clinical Dermatology, Common and Serious Diseases, Fitzpatrick et al., McGraw-Hill, Inc., Second Edition (1992), page 40-41. On the other hand, an ulcer is "a skin defect in which there has been a loss of the epidermis and the upper papillary layer of the dermis". Exhibit 2: Id., at page 771. Thus, the "lesion" disclosed by the Binder reference is not an equivalent of the "ulcer" feature of the present claims. Accordingly, the claims are novel over the Binder reference.

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Claims 6, 8 and 11 are newly rejected under 35 U.S.C. § 102(b) as allegedly being inherently anticipated by the Binder reference (U.S. Patent No. 5,670,484). Specifically, the Office Action alleges that the Binder reference "has the same method steps and the same end point as that of the Applicant. [Therefore, it] would inherently treat warts." The Office Action at page 7. Applicant respectfully asserts that the Office Action has misapplied the law of inherency. The MPEP §2112 (IV) states:

In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

(emphasis in original). Further, the MPEP §2112 (IV) states:

To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)...

(emphasis added). The claims are directed to the administration of botulinum toxin to treat a particular skin disorder that has been diagnosed/identified, and the claims have been amended to recite "a patient in need thereof" to clarify this feature. Accordingly, the claimed invention requires a step of diagnosing/identifying a patient with a specific skin disorder (i.e., warts) and administering botulinum toxin to treat that skin disorder. The Binder reference does not disclose the step of diagnosing/identifying a patient with warts and thereby administering botulinum toxin to treat the warts. Further, the step of diagnosing/identifying a patient with warts and thereby administering botulinum toxin to treat the warts does not necessarily flow from the teachings of the Binder reference, which teaches administering botulinum toxin to treat the cutaneous cell-proliferative disorder (i.e., psoriasis lesion and dermatitis lesion).

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Claim 11 is newly rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent Application Publication 2004/0087893 A1 (hereinafter “the Kwon reference”). The Office Action alleges that the Kwon reference discloses a method of administering a botulinum toxin for treating warts at page 6, section 0077.

Contrary to this allegation, the Kwon reference does not disclose a method of administering a botulinum toxin for treating warts. The Kwon reference discloses a solid drug solution perforator (SSP) system and an associated drug reservoir for delivering therapeutic, prophylactic and/or cosmetic compounds, for nutrient delivery and for drug targeting. With regard to page 6, section 0077, of the Kwon reference, it reads:

Another area of applications is cosmeceutical. An SSP system including a patch can deliver botox toxin or a hydroxyacid more efficiently and safely to remove or reduce wrinkle formation and skin aging. The system is also useful for treating lesions or abnormal skin features, such as pimples, corns, warts, calluses, bunions, actinic keratoses and hard hyperkeratotic skin, which is often found on the face, arms, legs or feet.

As such, the Kwon reference teaches that botulinum toxin can be delivered by the SSP system. However, the Kwon reference only teaches that botulinum toxin can be delivered by the SSP system “to remove or reduce wrinkle formation and skin aging.” **The Kwon reference does not teach or suggest that botulinum toxin may be administered to treat warts.** In fact, the Kwon reference does not teach the use of any drug to treat warts. At most, the Kwon reference teaches that a medication known for treating warts (which does not include botulinum toxin) may be delivered by the SSP system to treat warts. Thus, the Kwon reference cannot anticipate the claimed inventions.

The Office Action also alleges that the Kwon reference inherently discloses a method of administering a botulinum toxin for treating warts. However, the Office Action has not established that the method of administering a botulinum toxin to treat warts *necessarily flows* from the teaching of the Kwon reference. The Kwon reference only teaches that the claimed SSP system may be used in combination with botulinum toxin to reduce wrinkle formation and skin aging. With regard to warts, the Kwon reference merely suggests that the claimed perforator system may be used in combination

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with a drug to treat warts. Perhaps the Office Action is suggesting that there is a **probability or possibility** that the claimed perforator system may be used in combination with a botulinum toxin to treat warts. In this respect, Applicant respectfully directs the Office to the MPEP sections cited above, which states that inherency may not be established by probabilities or possibilities. The claimed method of administering a botulinum toxin to treat warts must *necessarily flows* from the teaching of the Kwon reference—which it does not. Accordingly, the Office Action has not met the requirements for establishing that the Kwon reference inherently anticipates the claimed invention. Thus, the claimed invention is novel over the Kwon reference.

In view of the foregoing, Applicant submits that the pending claims are in condition for allowance, and an early Office Action to that effect is earnestly solicited.

Respectfully submitted,



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Letters to the Editor 507

Botulinum Toxin and Rhinorrhea

To the Editor:

I read with great interest the results of Shaari et al.'s study.¹ Using a dog model, they demonstrated that topical application of botulinum toxin type A to the nasal mucosa inhibits nerve-evoked secretions.¹ These results offer yet another therapeutic potential for botulinum toxin, as an alternative treatment in vasomotor rhinitis.

The authors proposed the injection of the sphenopalatine ganglion as a more effective way of delivering the toxin to the nasal glands. Direct submucosal injection of botulinum toxin is likely to produce more control of mucosal secretions. The injected dose is likely to spread locally, producing a field of selective denervation of the nasal seromucinous glands. The size of this regional denervation field is proportional to the dose injected. From our studies using subcutaneous injections of botulinum toxin to block the cholinergic sympathetic fibers to sweat glands, we found that one-point injection of 20 U of (Dysport-Porton Products, U.K.) in the dorsum of the hand produces a circular area of complete anhidrosis 5 to 6 cm in diameter.^{2,3} Unlike the proposed sphenopalatine injections, direct submucosal injections are less likely to produce dry eyes.

Of the four dogs studied, one had a paradoxical response with increased secretions. Although this can be attributed to inadequate stimulation of the control side or failure of the toxin to penetrate the mucosa, a "true paradoxical effect" of the toxin cannot be ruled out.⁴ Excessive salivation has been known to occur in botulism.⁵ A similar paradoxical effect on lacrimal glands, producing watering of the eyes, has been reported in patients receiving periorbital injections for blepharospasm or hemifacial spasm.⁶ The paradoxical effect of the toxin on the "neuroglandular junction" remains unexplained.⁷ It may represent hypersensitivity of the denervated glands in a similar fashion to the well-known phenomenon of "paralytic secretion," in which excessive salivation occurs a few days after denervation of the salivary glands and persists for 2 to 3 weeks.⁸ The autonomic dysfunction in botulism out lasts skeletal muscle paralysis, indicating that the neuroglandular junctions require more time to recover. This has been our experience with botulinum toxin-induced anhidrosis, an effect that may last up to 11 months (Bushara, Unpublished observation, 1995).

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Surg 1996;114(3):507.

HF. Rhinorrhea is de-
on of botulinum toxin.
;112:566-71.

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2. Bushara KO, Park DM. Botulinum toxin and sweating. *J Neurol Neurosurg Psychiatr* 1994;57:1437-8.
3. Bushara KO, Jones JC, Park DM, Schutta HS. Botulinum toxin and sweating [Abstract]. *Mov Disord* 1995;10:391.
4. Bushara KO. Localised autonomic failure due to botulinum toxin injection. *J Neurol Neurosurg Psychiatr* 1995;59:105.
5. Dickson EC, Shevky R. Studies on the manner in which the toxin of clostridium botulinum acts upon the body. I. The effect upon the autonomic nervous system. *J Exp Med* 1923; 37:711-31.
6. Klara HK, Magoon EH. Side effects of use of botulinum toxin for treatment of benign essential blepharospasm and hemifacial spasm. *Ophthalmic Surg* 1990;21:335-8.
7. Kuntz A. Innervation of cephalic autonomic effectors. In: Kuntz A, ed. *The autonomic nervous system*. Philadelphia: Lea & Febiger, 1945:335-56.

Autoimmune Inner Ear Disease

I could not let the *Letter to the Editor* that appeared in The JOURNAL (Boyles JH Jr. 1995;112:631-3) go without comment. It was difficult to believe the author had not removed his blinders and failed to site the literature of current investigation by Harris¹⁻⁴ and Moscicki⁵⁻⁹ and previous articles by McCabe.¹⁰⁻¹² No one refutes the possible role of allergy in fluctuating sensorineural hearing loss. But, get real; if one is going to stand on a publishing soap box and spout disparaging statements about others and then tout one's own philosophies without the facts, that's bad journalism.

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REFERENCES

1. Ryan AF, Harris JP, Schiff M. Immunology of the ear: experimental models. In: Veldman, McCabe BH, eds. *Otoimmunology*. Amsterdam: Kugler Press, 1987:187-92.
2. Harris JP. Immunopathology of the inner ear. In: Ogra P, Bernstein J, eds. *Immunology of the ear*. New York: Raven Press, 1987:437-51.
3. Harris JP. The endolymphatic sac: its importance as a site of inner ear host defense and immunity. In: Nadol JB, ed. *Proceedings of the second international symposium on Ménière's disease*. Amsterdam: Kugler and Ghedini Publications, 1989.
4. Harris JP. Experimental immunology of the inner ear. In: Pfaltz CR, Arnold W, Kleinser O, eds. *Bearing of basic research on clinical otolaryngology. Advances in otorhinolaryngology*. Basel: Karger, 1991:46:26-33.
5. Harris JP. Clinical and experimental aspects of immune-mediated sensorineural hearing loss. In: Veldman J, McCabe B, Harris J, eds. *Immunobiology in otology, rhinology and laryngology*. Alstelveen, The Netherlands: Kugler, 1992:45-9.
6. Harris JP. Immune-mediated diseases of the inner ear. In: Sharpe JA, Barber HO, eds. *The vestibulo-ocular reflex and vertigo*. New York: Raven Press, 1993:361-74.
7. Harris JP. Autoimmune diseases affecting the inner ear. In:

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